SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

New aspects of the management of severe haemostasis disorders: anticoagulant strategy in pregnancy with antithrombin deficiency, thromboembolism related to inflammatory bowel disease and acquired haemophilia

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The Examination takes place at the 2nd floor courtroom of Faculty of Public Health, University of Debrecen, at 12:00, 21 December, 2015.

Head of the **Defense Committee**:	Róza Ádány MD, PhD, DSc
Reviewers:	Szilvia Vad MD, PhD
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The PhD Defense takes place at the Lecture Hall of Building „A", Department of Internal Medicine, Faculty of Medicine, University of Debrecen, at 2:00 pm, 21 December, 2015.

INTRODUCTION

Thrombophilia is a hypercoagulable state which is likely to predispose to the development of venous thromboembolism (VTE). Over the past decades, there have been great advances in the understanding of the pathogenesis of VTE. Nevertheless, a number of questions remained unanswered. It is known that some subjects carrying several risk factors for VTE will never experience a thrombotic event while other individuals developed recurrent thromboembolic (TE) episodes without known risk factor. Thrombophilias may be inherited, acquired or both types can coexist (mixed). The risk of VTE can differ according to each abnormality.

The identification of the mutations leading to the decrease of the natural anticoagulant proteins result in the better understanding of the development of VTE. It turned out that the thrombophilias are highly heterogenous, in case of antithrombin (AT) deficiency the known pathogen mutations have exceeded 250.

The clinical and epidemiological studies on thrombophilias revealed the multifactorial nature of VTE, which development is a result of the interaction of gene/gene and/or gene/environmental risk factors. By this model, the inherited thrombophilia is in interaction with other well defined VTE risk factors, as follows: active cancer, inflammatory conditions, surgery, trauma, immobility, use of oral contraceptives, hormone replacement therapy, obesity, antiphospholipid antibodies (APAs), pregnancy and puerperium, sepsis, malformations of the veins and advanced age. This dynamic model of the pathogenesis of VTE takes account of the genetic architecture of thrombophilia and the interaction of the potentially reversible or preventable acquired environmental risk factors. On the basis of family studies it is known that in individuals carrying various thrombophilias the risk of the development of a VTE event is different. In individuals with the deficiency of AT, protein C (PC) and protein S (PS), the homozygous mutations of Factor V Leiden (FV Leiden) or prothrombin (FII) G20210A and the combined thrombophilias the thrombotic risk is high, while the heterozygous form of FV

Leiden or FIIG20210A mutation results in lower risk to develope a VTE event compared to subjects free of these defects.

Among acquired risk factors to VTE, pregnancy is of great importance. In pregnancy the risk of VTE is increased. In patients with pregnancy who already experienced a VTE episode the risk of placenta-mediated pregnancy complications is increased. Among inherited thrombophilias, the high risk thrombophilias and the antiphospholipid syndrome (APS) increase the risk of the development of VTE during pregnancy and the risk of pregnancy-loss is also higher. There is a higher incidence of late pregnancy complications like pre-eclampsia, stillbirth, intrauterine growth restriction (IUGR), placental abruption and haemolysis, elevated liver enzymes and low platelet count syndrome (HELLP). In case of the AT deficiency which represents the highest risk to VTE there are only few data with regards to the management and the prophylaxis of VTE during pregnancy.

From other acquired thrombophilic states, the increased risk of TE related to inflammatory bowel disease (IBD) – especially to it's active form – should be outlined, as it is a significant cause of morbidity and mortality of patients with IBD. There are few data about the anticoagulant and thrombolytic management of patients with active IBD and acute TE.

Among severe haemostasis disorders in clinical practice the rare and severe bleeding disorder, the acquired haemophilia A (AHA) represents a high challenge. Either the diagnostics or the management is complex and particularly difficult in case of patients with high inhibitor titer.

Inherited AT and pregnancy

AT is a natural anticoagulant and its primary action is to inhibit thrombin mediated fibrin clot formation and generation of thrombin by FXa. AT-deficiency is a rare and the most thrombogenic type of thrombophilia with a 25-50 fold increase of relative risk of VTE in the general population.

Mutations of the AT gene can cause defects in the reactive site (type II RS), heparin binding site (type II HBS) or can generate a pleiotropic effect (type II PE). Compared to type II RS and PE deficiency, the defects of the HBS are associated with a lower thrombotic diathesis and can be present in the homozygous form. A well described type II HBS defect is known as Budapest mutation. The homozygous type II HBS defect with low levels of activity is associated with severe venous and arterial thrombosis and recurrent pregnancy loss.

In pregnant women with thrombophilia, especially with AT deficiency decreased activity of the anticoagulant system may lead to deteriorated placental circulation and adverse pregnancy outcome (APO). Maternal AT deficiency has an estimated 6-fold increased risk of thromboembolic complications and a markedly increased risk of fetal loss. An increased risk of late pregnancy complications like pre-eclampsia, stillbirth, IUGR, placental abruption and HELLP is also associated with patients with AT deficiency and pregnancy.

Treatment guidelines are inconsistent with regards to management of patients with AT deficiency and pregnancy. Owing to its rarity, therapeutic approaches are mainly based on case reports published in the literature.

TE related to IBD

Crohn's disease (CD) and ulcerative colitis (UC) the two main forms of IBD are systemic disorders often associated with extraintestinal manifestations, complications, and other immune mediated disorders. These chronic inflammatory conditions are characterized by a hypercoagulable state and prothrombotic condition, and accompanied by abnormalities in coagulation. Recent data suggest that TE is a disease-specific extraintestinal manifestation of IBD, which develops as the result of multiple interactions between acquired and genetic risk factors. The incidence of systemic thromboembolic events in IBD patients ranges from 1%–7.7%, patients having a 3-4-fold overall increase risk for venous VTE compared to control population.

The application of anticoagulant and thrombolytic therapy in severe IBD is an unresolved issue. Generally the management of TE in IBD patients does not differ from treatment in non-IBD patients, although there are currently no clear guidelines for the management of IBD-related TE.

AHA

AHA is a rare disorder caused by the development of IgG-type autoantibody against clotting factor VIII. It occurs mainly in adults and the bleeding is often severe or life-threatening. AHA is an extremely rare event with an estimated incidence of 0.2-1.0 cases of million population/year. The aetiology of the disease is unknown: autoimmune diseases, malignancies, drugs, skin diseases and pregnancy may promote the development of an inhibitor but it can also appear in healthy persons. In approximately 50% of the patients the condition is classified as idiopathic since no underlying disease can be detected. AHA is a severe haemorrhagic diathesis characterized by extensive flat subcutaneous and intramuscular haematomas. The disease is associated with a high mortality rate, varying from 8% to 22% .

In AHA with high inhibitor titer the eradication therapy is particularly difficult. Patients with high inhibitor titer to FVIII respond less frequently to immunosuppression. Two aims have to be achieved in the management of AHA: 1) To treat the acute bleeding, and 2) to eradicate the FVIII autoantibody.

There is an extensive literature about the disease, but only few controlled data are available.

OBJECTIVES

- To evaluate management, maternal and fetal outcomes in patients with heritable AT deficiency and pregnancy treated with our individualized anticoagulant protocol. We retrospectively analysed data of patients with inherited AT deficiency and pregnancy managed between 2012 and 2014 in the Center of Thrombosis and Haemostasis, Department of Internal Medicine, Faculty of Medicine, University of Debrecen.
- To present and analyse the anticoagulant and thrombolytic treatment in a patient with acute arterial TE related to active IBD.
- To demonstrate our salvage protocol for the eradication of autoantibodies in an AHA patient with high inhibitor titer.

PATIENTS, MATERIALS AND METHODS

Retrospective evaluation of patients with AT deficiency and pregnancy

Study design, setting

A retrospective observational study was performed to evaluate management, thrombotic events, maternal and pregnancy outcomes in women with hereditary AT deficiency managed in our center.

Study population

Between 2012 and 2014, five patients with hereditary AT deficiency and pregnancy were included.

Methods

Collection of data

We reviewed anamnestic data, medical history, information regarding previous pregnancies, treatment before, and during pregnancy and postpartally, thrombotic events, and maternal and fetal outcome.

Thrombophilia screening

Testing for Factor V Leiden mutation and FII polymorphism was performed and APAs were screened in patients with a history of a previous VTE or recurrent pregnancy loss. PC and PS evaluations were omitted in an attempt to prevent the possibility of a false positive result.

AT gene sequencing

AT deficiency was confirmed by the fluorescent DNA sequencing method.

AT measurements

AT activity measurements were performed daily at the beginning of the therapy and were checked monthly throughout the pregnancy. AT activity was evaluated just before (trough) and after 4 hours of infusion (peak) of ATC. In cases one and two Antithrombin III (Baxter), in cases three to five Kybernin P (CSL Behring) was used. AT activity was assessed with heparin

cofactor assay measuring FXa inhibition (Innovance AT, Siemens). AT antigen was measured with the immunonephelometric method (BN ProSpec system AT-III, Siemens). The reference interval of AT activity is 80-120% of the normal range.

Anti-FXa monitoring

Measurement of the low-molecular-weight heparin (LMWH) levels was performed by using FXa and its chromogenic substrate. Anti-FXa assessments were performed daily at the beginning of therapy or in case of dose adjustment and were regularly monthly checked throughout pregnancy. Anti-FXa levels were evaluated just before (trough) and 4 hours after injection of (peak) enoxaparin (Clexane, Sanofi). Reference ranges for the LMWH therapy were defined as prophylactic (0.2-0.5 IU/mL) and therapeutic (0.5-1.2 IU/ml).

Management protocol

Preconceptional period

Patients who were on acenocumarol or warfarin treatment were immediately switched to enoxaparin. Women without anticoagulant therapy were put on enoxaparin as soon as their pregnancy test became positive. In one case, anticoagulation started at the 23rd gestational week.

Gestation

Patients were checked monthly by a haemostasis-specialized haematologist in collaboration with an obstetrician experienced in management of patients with pregnancy and thrombophilia. Treatment protocol was based on the patients' thrombotic risk, described by the family history of VTE, presence of a previous thromboembolic event and a history of APO. The type of inheritance was also taken into account; homozygous type II „Budapest" AT mutation was considered as a factor resulting in a high risk for thrombotic events. Combined thrombophilia, like Factor V Leiden heterozygous mutation and AT deficiency were also considered as a high risk. In case of women with low risk, 40 mg of enoxaparin was given once a day at the start,

for high-risk patients, 1mg/bwkg of enoxaparin was prescribed twice a day in a form of a subcutaneous injection. LMWH administration was guided by the measurements of anti-FXa levels, in accordance with recommendations. Our aim was to reach prophylactic trough levels of anti-FXa in all cases and to achieve therapeutic peak levels of anti-FXa in women with a high thrombotic risk. If the targeted anti-FXa level was not achieved despite the increased dose of enoxaparin, AT concentrate (ATC) was initiated. Infusion of ATC was started at a daily dose of 30-50 IU/bwkg (calculated from [100-baseline activity]/1.6) to achieve 100% of activity as there are no general recommendations or guidelines to monitor the treatment. For maintenance ATC was administered three times per week. Trough and peak AT activity measurements were regularly performed but in fact, ATC dosing was guided by anti-FXa activities.

Delivery

At delivery LMWH was withheld at least 12 hours before labour or caesarean section and 30-50 IU/bwkg of ATC was given daily for two consecutive days.

Postpartum period

After post-delivery bleeding ended, enoxaparin was readministered and switched to acenocumarol or warfarin therapy. Patients with no history of VTE received 1 mg/bwkg of enoxaparin twice a day for 6 weeks. In case of patients with previous or gestational VTE enoxaparin was switched to either acenocumarol or warfarin (target INR: 2.0-3.0).

Follow-up

Patients were monthly checked for three more months postpartally.

Statistical analysis

Data are expressed as mean ± SD. Statistical analysis was done with GraphPad Prism 5 software (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Retrospective evaluation of patients with AT deficiency and pregnancy

A total of nine pregnancies of five women with hereditary AT deficiency were reviewed. The women ranged in age from 19 to 32 years [23.2 ± 4.2 (mean ± SD)]. Four of the five mothers were classified as high risk for a thrombotic event. History of fetal loss was found in two cases, and spontaneous abortion was observed, despite the heparin prophylaxis, in one case. All patients were put on enoxaparin upon the recognition of pregnancy. Four women required ATC to reach the targeted anti-FXa effect.

Laboratory findings

Three patients had homozygous type II HBS mutations (Budapest 3), two had type I heterozygous mutations of SERPINC1, and two patients also had an additional FV Leiden heterozygous mutation. The patients with homozygous type II mutations had seriously decreased AT levels (12-17%). The targeted anti-FXa levels were attainable except in one non-compliant case (3rd pregnancy of case 3).

Discrepancies from treatment protocol

In one case the patient was non-compliant which resulted in no further dose change in anticoagulant therapy despite the inappropriate anti-FXa effects. In another case LMWH was started when the patient presented with a right femoral deep vein thrombosis (DVT) and pregnancy in the 23rd gestational week. In this case, assessments were performed monthly in the local hospital due to the notable distance of the patient's home. Results were consulted by telephone.

Maternal outcome

Two mothers experienced VTE during pregnancy without prophylaxis, including one non-massive pulmonary embolism (PE) and a right femoral DVT. One patient with Budapest 3 homozygous AT mutation had a DVT despite the LMWH prophylaxis. All patients recovered.

With adequate anticoagulant therapy no maternal VTE, pre-eclampsia, eclampsia, placental abruption or HELLP syndrome were observed.

Neonatal outcome

Without effective anticoagulant prophylaxis, pregnancies ended with one early- and two late miscarriages in cases of mothers with type II HBS AT mutations. Under anticoagulant therapy from six gestations four healthy babies were born, three at terminuses and one at gestational week 32. The preterm delivery was forced by the mother who denied further anticoagulant therapy. Histology of the placenta found normal structure. Two fetal losses occurred on gestational weeks 13 and 28 in cases of two mothers with homozygous type II HBS AT mutations despite the anticoagulant therapy. Histology showed normal chorionic structure in case of the early miscarriage. In contrast, examination of the placenta revealed microthromboses and placental degeneration in case of the late pregnancy loss. No IUGR or stillbirth was observed.

Thrombolytic treatment in a patient with acute arterial TE related to active IBD

A 46-year-old male with a past medical history of 10 years' Crohn colitis, was presented with symptoms of relapse of IBD: weight loss, lower abdominal pain, bloody diarrhoea and arthralgia (Crohn's disease activity index: 345). He was treated with high dose prednisone due to severe activity of IBD one year before this event. Actually he was on a treatment with azathioprine (2,5 mg/bwkg) and mesalazine (3 g/day), on a stable dose during the last 1 year. He also complained about an acute onset of pain and coldness of his right hand. The physical examination revealed an acute arterial occlusion of the right hand. No provoking factor could have been detected. The color-Doppler imaging and the angiography proved the acute occlusion of the right brachial and radial artery. Vascular surgery intervention was not applicable. The laboratory findings showed anaemia (haemoglobin was 85 g/L) and thrombocytosis (platelet count was 409 G/l normal 150-400 G/l), the D-dimer test was positive (1.0 normal < 0.5 Feu/ul).

Liver and kidney panels were normal. An acutely performed endoscopy showed extended, severe inflammation of the colon with deep ulcers and signs of chronic activity involving the sigmoid colon. Considering the severity of the occlusion and the risk of a potential limb-loss catheter-directed thrombolysis (CDT) was suggested, despite the severe endoscopic findings, frequent bloody stools and moderate anemia. After 24 hours from onset of symptoms of arterial occlusion endovascular arterial intervention 5 mg bolus of recombinant tissue plasminogen activator (rt-PA) (Actylise injection, Boehringer Ingelheim International) was injected into the thrombus, followed by a continuous rt- PA infusion through the catheter in a dose of 0.1 mg/bwkg per hour. The treatment was carried on for 9 hours and proceeded with enoxaparin (60 mg QD, subcutaneously). The pain and coldness quickly decreased, the radial pulse became palpable. The control angiography proved the improvement. Despite the high risk of bleed no bleeding complication was observed. Echocardiography found no source of an embolus. LMWH prophylaxis was applied for 3 months (enoxaparin, 60 mg OD, subcutaneously). No congenital thrombophilia was proved (AT:120% normal:80-120; PC:132 % normal:70-130; PS:93 % normal:60-140; activated PC resistance: 2.51 normal:>2; FV Leiden: wild type; FIIG20210A:wild type, FVIII:188% normal:60-150). Neither lupus anticoagulant nor APA was detectable. The level of homocystein was also normal. The relapse of the CD was treated with anti-TNF-alpha antibody (infliximab). One year after the biological treatment and continuous LMWH prophylaxis the patient is in remission of IBD and has a complete recovery of the right upper limb arterial circulation.

Management of a patient with AHA

In February 2003 a 75-year-old male was hospitalized with large subcutaneous haematomas. His medical history did not indicate any inherited bleeding disorder. Laboratory evaluation revealed a prolonged activated partial thromboplastin time (APTT>100 seconds). Addition of normal plasma failed to correct the APTT. Prothrombin time (PT) and thrombin time (TT) were

normal. FVIII:C activity was below 1% while the other coagulation factors showed normal activity. AHA was diagnosed. No underlying condition was found. The titer of the antibody was high, 180-350 BU. He was admitted many times to our department between February 2003 and July 2005 with extensive spontaneous skin bleedings, intramuscular haematomas, extensive retroperitoneal haematomas, haemarthroses of knee, elbow and shoulder. The acute bleeding events were successfully managed either with rFVIIa (NovoSeven, Novo Nordisk) at a dose 110 ug/kg/3 hours or with FEIBA (Baxter) at a dose 75 IU/kg/12 hours until cessation of bleeding.

For eradication we consecutively used: 1) „Budapest" protocol; 2) Cyclosporine (Sandimmun Neoral, Novartis) 3x100 mg/day orally was started in September 2003 but it had to be stopped because of gastrointestinal intolerance; 3) in January 2005 a treatment with an anti-CD20 monoclonal antibody, rituximab (Mabthera, Roche) 375 mg/m^2 intravenously weekly for four weeks was initiated, but was also ineffective. The inhibitor titer remained constantly high.

In August 2005 a new type of eradication therapy was initiated. It was based on the VAD protocol (vincristine, adriamycin, dexamethasone), which is widely accepted for treating patients with multiple myeloma. A VWF containing FVIII concentrate was added to achieve immune tolerance. For eradication it was combined with VWF containing FVIII infusions. The following regimen was used: Vincristine 0.5 mg was administered in 100 ml NaCl 0.9% by an intravenous rapid infusion (30-60 minutes) on days 1-4, dexamethasone intravenously 40 mg on days 1-4, 9-12, 17-20, Haemate-P (Aventis Behring) FVIII/VWF concentrate infusions 20 IU/kg on days 1-4, 9-12, 17-20. Adriamycin was omitted because of its toxicity. Using this protocol the titer of FVIII antibody decreased rapidly and by the day 21 no inhibitor was detectable. FVIII:C activity and APTT normalized accordingly. Two months later, when autoantibody appeared again (53 BU), the protocol was repeated with the same results. The inhibitor disappeared (APTT:35 seconds and no prolongation was observed after incubation on

37C for two hours, FVIII:C>100%, FVIII inhibitor titer<1.0 BU). Although the effect was only temporary, the inhibitor-free period was long enough to carry out the operation of a large, painful inguinal hernia without factor replacement. No side-effects were observed.

DISCUSSION

Retrospective evaluation of patients with AT deficiency and pregnancy

In our study on patients with AT deficiency and pregnancy we experienced a high rate of maternal VTE, especially in cases with homozygous type II HBS mutations. Our data are in accordance with the citations reporting that AT deficiency and pregnancy are associated with a high risk of VTE. Our findings suggest that the type of AT deficiency may play an important role in creating a high risk phenotype, as is reported in cases of homozygous type II HBS mutations, and support the requirement of thromboprophylaxis in the prevention of maternal thrombotic complications in patients with AT deficiency.

In contrast to the literature reporting on the association of thrombophilia and the risk of a poor pregnancy outcome, systematic reviews found a conflicting relationship, or even failed to find an association between AT deficiency and APO. Although AT deficiency has a known heterogenous genetic background configuring different phenotypes, case series did not differentiate between the types of AT deficiencies and the levels of activity from the aspect of risk of VTE and pregnancy outcomes. In one study, authors did not find relationship between AT activity and pregnancy outcome although the lowest AT activity was 30%.

In the present study, mothers with the homozygous type II HBS mutation and the lowest AT activity produced the highest rates of miscarriage and maternal VTE. These findings are in accordance with the case reports and support the notion that AT deficiency increases the risk of placenta-mediated pregnancy complications. Adequate anticoagulant therapy may prevent vascular lesions in the placenta caused by a high risk thrombophilia like AT deficiency.

Data concerning the association between late pregnancy complications and AT deficiency are contradictory. Some authors reported a higher prevalence of AT deficiency among patients with late pregnancy complications, which in the present study were not observed.

Despite the fact that AT deficiency is considered as a high risk thrombophilia, treatment guidelines recommend only ante- and postpartum LMWH prophylaxis or even just antenatal vigilance and postpartum LMWH prophylaxis in cases of AT deficiency without a history of maternal VTE. These guidelines classifying AT deficient women into high or moderately increased risk of VTE on the basis of family and personal history of VTE do not differentiate between the certain types and do not take into account the severity in the decrease of AT activity. In contrast, many authors report on the association of high incidence of maternal thrombotic and fetal complications in cases of homozygous type II HBS AT deficiency and pregnancy with a seriously diminished AT activity. In fact, we observed a strong association between the type and severity of AT deficiency and the incidence of maternal and fetal complications. Our data underline the clinical importance of the distinction between type II-HBS and other type of AT deficiencies as well as between the homozygous and heterozygous forms. Hence when AT gene sequencing is not available, concomitant determination of progressive anti-FXa and heparin cofactor anti-FXa activities can help to diagnose the type II-HBS AT deficiency and distinguish between homozygotes and heterozygotes.

Although current guidelines do not recommend using ATC even in high risk patients with pregnancy requiring therapeutic anticoagulation many case reports and observational studies found a better pregnancy outcome with the use of LMWH and ATC together. Our data support in conjunction with citations above, the necessity of therapeutic anticoagulation of high risk patients.

Our study has a number of strengths. To our knowledge, there are only two cases of homozygous type II HBS AT deficiency with successful pregnancy outcome reported until now. This is the first paper to report three expectant mothers with homozygous type II HBS AT mutations. They had two successful deliveries treated with our anticoagulant protocol. The novel aspect of our study is that a risk-adopted individualized anticoagulant protocol was used

based on clinical risk assessment and mutation analysis. The potential limitation of our study could be its single center design and a relatively small number of cases due to the low prevalence of AT deficiency.

We concluded that since the risk of TE varies considerably between AT mutations, to assess patient's perceived level of risk - beyond the familiar and personal VTE history - the type of AT deficiency and the underlying mutation should be taken into account. We found that AT deficiency is associated with a high risk of maternal VTE and frequent pregnancy complications, which support the need of risk-adopted anticoagulant therapy.

Thrombolytic treatment in a patient with acute arterial TE related to active IBD

We report a case of a peripheral arterial TE of the right upper limb in a 46-year-old patient with acute relapse of CD. In the background no provoking factors could have been detected. Thrombophilia evaluation was normal and a source of an embolus was undetectable either. The background of the hypercoagulability that is present in IBD is the altered platelet/endothel cell function and interaction, the elevated level of coagulation factors and the decreased activity of fibrinolysis. In patients with IBD the prevalence of thrombosis is 6,2%, the average incidence of TE is 3,6 times higher compared to normal population. TE events occur mainly in the venous circulation, but can also develop in the arterial circulation. DVT and PE are the most common types of TE, but thromboses are also reported in unusual sites such as cerebral, innominate, retinal, hepatic, and mesenteric veins. Arterial thromboembolic complications occur less frequently and the majority of cases seem to occur post-surgery. Patients with IBD have a markedly increased risk of acute mesenteric ischemia. IBD patients are more likely to have cardiac arterial thromboembolic disease, regardless of diagnosis or sex. CD has an increased risk for cerebral arterial thromboembolic disease with some differences regarding the gender. While the risk of gastrointestinal bleeding has to be considered in each case, most patients tolerate anticoagulants at full dose. Thrombolytic therapy is generally preserved for massive,

life-threatening thrombosis. So far, only 17 cases of local thrombolytic treatment in IBD patient have been reported. Until now there has been no case reported on upper limb arterial occlusion and CDT in IBD. In conclusion, moderate-severe active CD has to be considered as a risk factor for systemic TE. Practice guidelines strongly recommend the use of thrombosis-prophylaxis in active IBD. Arterial thrombosis is a rare, but severe complication of IBD. Considering the severity of the occlusion, in cases of life-threatening TE, CDT could be an effective and safe intervention.

Management of a patient with AHA

The eradication of the autoantibodies in AH is often difficult. In our case the applied immune therapeutic interventions remained unsuccessful. Many reports have described various methods to decrease or eliminate FVIII inhibitors in non-haemophilic patients. Immunosuppression with steroids, cyclophosphamide or cyclosporine and rituximab are reported to be effective for the eradication of the inhibitor. In our case the applied therapeutic interventions remained unsuccessful. In contrast to others, rituximab was also ineffective. A modified VAD protocol was applied. Lian et al. have produced remarkable results treating AH patients with FVIII infusions combined with CVP (cyclophosphamide, vincristine, prednisone). Twelve non-haemophilic patients were treated, and the inhibitor disappeared except for one case who had a high titer of inhibitor to FVIII (44-139 BU). In our protocol immunosuppression with vincristine and dexamethasone was completed with FVIII/VWF (von Willebrand Factor) concentrate (Haemate P). The theoretical background of the application of a FVIII concentrate is the stimulation and acceleration of lymphocyte proliferation.

Nowadays some investigators support the view that FVIII concentrates containing VWF can be more successful in achieving immune tolerance than the pure FVIII concentrates. High dose of dexamethasone induces the apoptosis of plasma cells, and seems to be more effective than methyl-prednisone. Vincristine, a potent immunosuppressive agent is supposed to have an

additive effect. This protocol eradicated the inhibitor twice in our patient. The effect was only temporary (1-2 months), but the inhibitor-free period was enough for a surgical intervention. The operation was made without any plasma substitution, and bleeding tendency was not observed. The treatment was simple, effective, relatively short (4 days repeated three times) and inexpensive. Side-effects were not recorded. In conclusion, our result indicate that the use of this protocol might be considered as a salvage treatment in therapy-resistant AH patients with high inhibitor titer for temporary eradication of autoantibodies. As our observation is based on a single case, the treatment of a larger number of patients is necessary to provide stronger evidence on the effectivity of this regime and to clarify the role of each component in the protocol.

SUMMARY – NEW CONCLUSIONS

Retrospective evaluation of patients with AT deficiency and pregnancy

- We retrospectively evaluated nine pregnancies of five AT deficient women. On the basis of personal risk-assessment and the subtype, genotype and phenotype of the AT defect, we developed a new recommendation for the anticoagulant management of this high risk population.
- This is the first study to report on the management of three expectant mothers with homozygous Budapest 3 type II HBS AT mutations who had two successful deliveries treated with our individualized anticoagulant protocol.
- We found that AT deficiency, especially in cases of homozygous type II HBS AT mutations is associated with a high risk of maternal VTE and frequent pregnancy complications, which support the need for risk-adopted anticoagulant therapy.

Thrombolytic treatment in a patient with acute arterial TE related to active IBD

- This is the first case in the literature to report on a successful local intraarterial CDT in a patient with IBD and an acute upper limb arterial occlusion.
- Based on our findings we concluded that in active IBD ─ despite the increased risk of bleeding ─ in case of life-threatening TE, CDT could be an effective and safe intervention.

Management of a patient with AHA

- We also demonstrated the challenge of the treatment of an AHA patient with high inhibitor titer. We presented a new eradication protocol which was temporarily successful in the eradication of the inhibitor to FVIII.

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Candidate: Péter Ilonczai
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List of publications related to the dissertation

1. **Ilonczai, P.**, Oláh, Z., Selmeczi, A., Kerényi, A., Bereczky, Z., Póka, R., Schlammadinger, Á., Boda, Z.: Management and outcome of pregnancies in women with antithrombin deficiency: A single-center experience and review of literature.
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IF:1.403 (2014)

2. **Ilonczai, P.**, Tóth, J., Tóth, L., Altorjay, I., Boda, Z., Palatka, K.: Catheter-directed thrombolysis in inflammatory bowel diseases: Report of a case.
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5. Árokszállási, A., **Ilonczai, P.**, Rázsó, K., Oláh, Z., Bereczky, Z., Boda, Z., Schlammadinger, Á.: Acquired haemophilia: An often overlooked cause of bleeding - experience from a Hungarian tertiary care centre.
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Total IF of journals (all publications): 12,716
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